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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,132	07/07/2006	Sarah Donald	13566.105014	7292

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EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
05/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,132	DONALD ET AL.	
	Examiner	Art Unit	
	CHRIS E. SIMMONS	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-17 and 21-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-17 and 21-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20 February 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-17, 21-22, 24-30 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating breast cancer, ovarian cancer and endometrial cancer, does not reasonably provide enablement for treating tumors generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to treating tumors. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. The unpredictable nature of cancer assays has long been recognized. See, *e.g.*, Gura (*Science*, vol. 278, pp. 1041-1042 (1997)),

which provides an overview of the problems involved with sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile. Since formal screening began in 1955 many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (second paragraph of the article). As noted therein, the "fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." The reasons are many, including basic differences between human patients on the one hand, and animal and cell culture models on the other (third paragraph of the article). Specifically, Fayette et al. (The Oncologist, Vol. 10, No. 10, 827-832, November 2005) discloses at page 830, second column, 1st full paragraph, last sentence, that ET-743 was ineffective in gastrointestinal stromal tumor and in osteosarcoma.

An efficient means of predicting activity with *in vivo* models remains desirable for compounds with anti-proliferative activity *in vitro* to this day. See the abstract of Johnson et al., *British Journal of Cancer*, vol. 84(10), pp. 1424-1431 (2001). As noted at the bottom of page 1424, the current "drug screening and development scheme remains an empirical one." See also the first paragraph of the "Discussion" section at page 1430 wherein the authors state that "analysis of xenograft versus clinical results illustrates that a histology to histology comparison of these models to activity in the clinic cannot be reliably discerned for these 'empirically' selected compounds acting against non-molecularly characterized tumors."

Therapies targeted to the common mechanism of angiogenesis have been

tried as a means to overcoming the problems arising from the tremendous heterogeneity among different cancer types. Antiangiogenic therapies remain unpredictable, however, and have mainly failed due to numerous factors, including poor correlation between activity in rodent models and therapeutic efficacy in human patients; the tissue and/or tumor specific nature of vasculature; and the lack of a feasible means to monitor antiangiogenic response in patients. Due to these difficulties, additional markers associated with specific pathologies must further be identified, and even when there are no reasonable expectation of therapeutic success can be guaranteed (in part because drug delivery to the ischaemic site can be a major limiting factor, especially given the lack of tools with which to monitor site specific drug availability within the tumor). See Gupta et al., *Postgrad. Med. J.*, vol. 81, pp. 236-242 (2005) at the passage bridging the bottom of the lefthand column to the penultimate line on page 239.

As a result of such difficulties, different types of cancers must follow individualized strategies for angiogenesis based treatment. Consequently, most "treatments hold promise but will have to be clinically tested for different kinds and different stages of tumor growth." Gupta et al. at the lefthand column of page 240.

2. The breadth of the claims

The claims are very broad because they suggest the treatment of tumors generally.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for treating tumors, other than breast tumors. The latter is corroborated by the working examples.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to treat tumors generally as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

Claims 9-17 and 21 were rejected under 35 USC 103(a) as being unpatentable over Donald et al. (Cancer Research (2003); 63(18):5902-5908; in Applicant's IDS filed 04/07/2006) in view of US 2004/0108086 A1. **This rejection is maintained and is now applicable to newly added claims 22-32.**

As an initial matter, the rejection relies on the May 10, 2002 publication date of WO 2002/36135, which is the PCT application from which Takahashi (US 2004/0108086) entered the national phase.

Applicant argues that the claimed composition illustrates unexpected hepatoprotection against hepatotoxicity induced by ET-743. However, a proper side-by-side comparison of the closest prior art and the instant invention is not described in the instant specification to illustrate unexpected hepatoprotection from ET-743 toxicity. Accordingly, it is submitted that one cannot determine that I3C unexpectedly protects the liver from ET-7453 toxicity.

Applicant asserts that the specification and literature provide reports of actual failure in reducing the hepatotoxic effects of by administering hepatoprotectors of various classes. Thus, both the specification and the scientific literature provide evidence negating an expectation of success. The examiner does not find this assertion to be persuasive because both the specification (1st full paragraph at page 6) and the literature (Donald et al. cited by applicant (abstract)) acknowledges that dexamethasone is effective in protecting the liver from the toxic side effects induced by ET-743. It would appear that others did not fail at protecting the liver from the hepatotoxic effects induced by ET-743 since dexamethasone is disclosed in the prior art and acknowledge by applicant as a liver protector of ET-743 hepatotoxicity. Accordingly, applicant's assertion that others have failed is not found to be persuasive.

At page 10 of the response, applicant argues that the references cited by the examiner do not suggest that the antitumor effectiveness of ET-743 can be maintained while administering I3C or one or more of its derivatives. It is submitted, however, that the legal standard for obviousness does not require that the reference make such a suggestion. All that Is needed is a reasonable expectation of success as motivation for combining the I3C and ET-743.

Applicant further asserts that I3C not only maintained the antitumor effects of ET-743, but actually improves tumor growth inhibition (TWI). Example 2 does not show that an unexpected improvement in TWI, however. An unexpected improvement would be an improvement that is more than an additive improvement of TWI when I3C and ET-743 are used together. However, the results indicate a less than additive improvement on TWI. When I3C and ET-743 were used alone, each caused a TWI of 43 % and 54 % decrease in tumor growth weight, respectively. When used together, the compounds only elicited a 71% weight reduction (instant specification at page 14, 1st full paragraph, last sentence). Accordingly, since the composition with the agents together elicited a TWI that was less than that of the additive TWI of the compositions containing the agents individually, it is not considered to show unexpected results.

As for the limitations in claims 24-30, particularly the administration of the indole compound 3 or 6 days prior to administering ET-743. It is disclosed in Donald et al. that dexamethasone can provide hepatoprotection when administered 3 days or 6 days prior to the administration of ET-743 (Table II). Since the reference further discloses that I3C was like dexamethasone when

tested, it would have been obvious to administer I3C 3 or 6 days prior to administration of ET-743. With regard to the amount of I3C administered, when the dexamethasone amount of 5-20 mg/kg is calculated to the human equivalent dose in amount per body surface area, the amount overlaps that claimed for I3C. Since the reference discloses that I3C was like dexamethasone in its ability to protect the liver, the amount is also suggested for I3C since one of ordinary skill in the art would be motivated by the reasonable expectation of success when using amounts similar to those used for dexamethasone.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/C. E. S./
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612